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Investigating the Effects of Metformin on Pyruvate Carboxylase

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Metformin is most commonly prescribed for the treatment of Type II diabetes, a disease in which the effects of insulin are desensitized leading to hyperglycemia. While the clinical effects of this generic drug are clearly established, the exact targets of metformin action remain unclear. The present study assesses the hypothesis that metformin lowers blood glucose through inhibition of pyruvate carboxylase, an anapleurotic enzyme involved in gluconeogenesis. Due to the relative low cost of metformin, it is widely accessible to communities around the world. Currently at 150 million per year, the number of users dependent on metformin for quality of life continues to rapidly increase. Thorough investigation of the drug and all possible targets involved in antidiabetic action becomes crucial. Thus, the purpose of this study is to further elucidate the mechanism of action for metformin, helping to further understand the adverse effects of taking the drug. Results of the study may help further explain conditions such as lactic acidosis, a common adverse effect of metformin described as painful and imparting pain of the extremities. The hypothesis will be addressed by measuring specific activity of purified bovine pyruvate carboxylase spectrophotometrically through loss of absorbance at 340nm following the oxidation of NADH. The design involves a series of enzyme-coupled assays treated with metformin above, below and near pharmacokinetically consistent concentrations (50-5,000 mM). All treated groups will consist of the enzyme and the buffer solution with metformin, while control groups will consist of the enzyme, buffer solution and no metformin. Activity between treated and control groups will be interpreted by linear rate models and analyzed through repeated measures analysis of variance. We expect metformin to have a significant inhibitory effect on pyruvate carboxylase at concentrations ranging from 200-500 μM, similar to concentrations found in the portal vein of the liver.